Studies on the Constituents of the Seeds of *Hernandia ovigera* L. VII.[1] Syntheses of (±)-Hernolactone and (±)-Hernandin

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Two new lignans, hernolactone (1) and hernandin (2), isolated from the seeds of *Hernandia ovigera* L. were synthesized in racemic forms. Firstly, (±)-1 was obtained by utilizing the conjugate addition reaction of 4 with butenolide followed by alkylation with trimethoxybenzyl bromide and subsequent removal of the protecting groups. Synthesis of 2 was pursued using the corresponding 4-phenyl-1,2-dihydronaphthalene lactone (18). The cleavage of the lactone moiety of 18 afforded an unsaturated hydroxy acid (22). Subsequent hydrogenation of 22 followed by acidification with concentrated hydrochloric acid gave isopicrohernandin (21), leaving the 2,3-*trans*, 3,4-*cis* hydroxy acid (23), which was lactonized by means of *N,N*-dicyclohexylcarbodiimide to afford (±)-2.

Keywords *Hernandia ovigera*; hernolactone; hernandin; lignan; dibenzylbutyrolactone lignan; phenyltetralin lignan; isopicrohernandin; Diels–Alder reaction

In the previous papers of this series,[1,2] the authors isolated nine lignans from the seeds of *Hernandia ovigera* L. collected in Okinawa and comfirmed their structures. Among them, hernolactone[1] (**1**) and hernandin[2b] (**2**) were new compounds and their structures were determined as (2*R*,3*R*)-3-(4′-hydroxy-3′,5′-dimethoxybenzyl)-2-(3″,4″,5″-trimethoxybenzyl)-γ-butyrolactone (**1**) and 5-methoxy-desoxypodophyllotoxin (**2**), respectively (Fig. 1). More recently, the latter was also found in *Hernandia cordigera*.[3]

This paper describes syntheses of the racemic forms of these two new lignans. The synthesis of (±)-hernolactone (**1**) was carried out according to the known procedure[4] shown in Chart 1.

Benzyl syringaldehyde (**3**) was converted to the corresponding phenyldithioacetal (**4**) followed by condensation with butenolide by Michael addition in the presence of *n*-butyllithium to give the lactone (**5**), which was alkylated with 3,4,5-trimethoxybenzyl bromide[5] using lithium hexamethyldisilylamide (LHDS)[4c] to afford compound **6**. By removal of the protecting groups of **6** with Raney nickel, (±)-**1** was obtained as needles, mp 116—118 °C. The spectral data were identical with those of natural **1**.

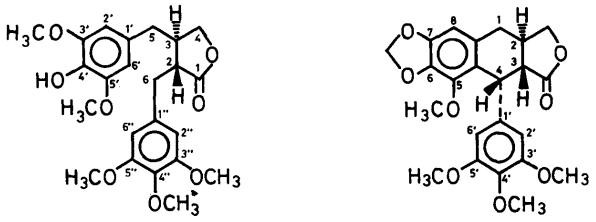


Fig. 1

Hernandin (**2**) is a new compound which belongs to the category of phenyltetralin-type lignans. Many studies have been reported on the synthesis of this type of lignans,[6] and some of them were obtained in connection with syntheses of steganacin[7] and deoxyschizandrin.[8] A route *via* an itaconic acid derivative, obtained by Stobbe condensation of a benzophenone derivative with diethyl succinate, followed by cyclization[9] was first undertaken through the sequence outlined in Chart 2.

However, various attempts to obtain **8** by condensation of **7** with 3,4,5-trimethoxybenzoic acid gave poor results, although a method employing Nafion-H[10] and polyphosphoric acid ester (PPE)[11] afforded **8** in low yield (below 30%) accompanied with a by-product **9**.[12] Moreover, the condensation of **8** with diethyl succinate to give **10** in the next step was unsuccessful.

Another method for the syntheses of phenyltetralin-type

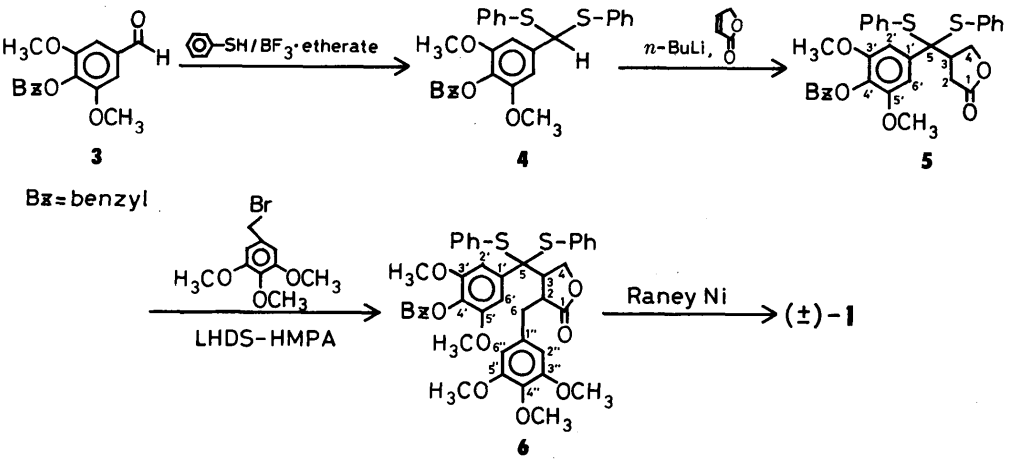


Chart 1

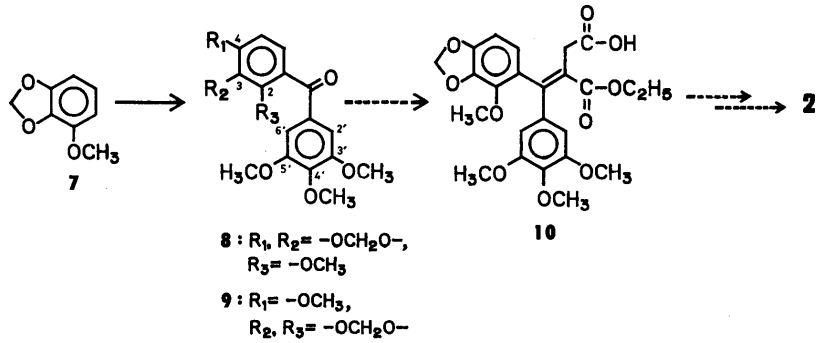
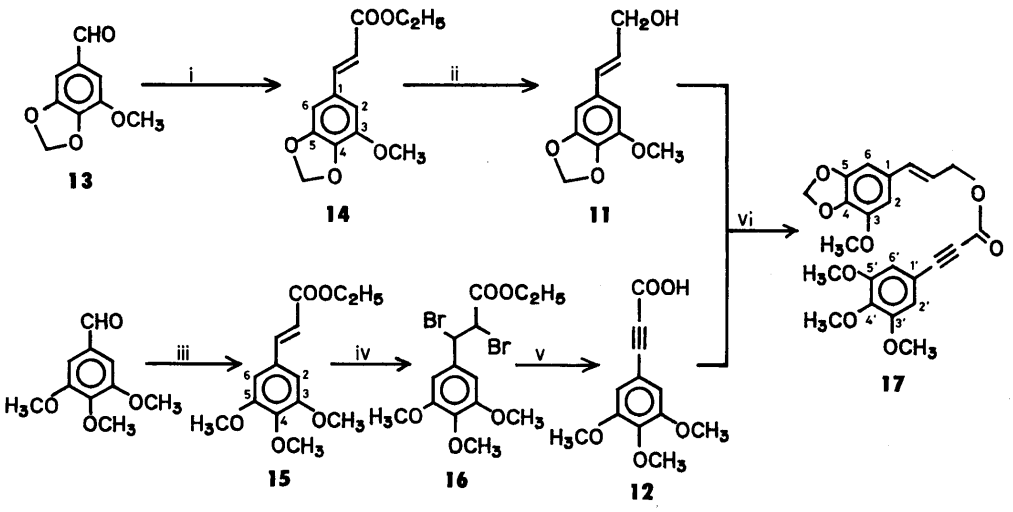


Chart 2



i, iii) $(EtO)_2P(O)CH_2COOEt$; ii) LAH; iv) Br_2; v) KOH; vi) DCC.

Chart 3

lignans, a route involving the condensation of two phenylpropanoid-type compounds followed by an intramolecular Diels–Alder reaction,[6a] was found to be applicable for the synthesis of hernandin (**2**).

3-Methoxy-4,5-methylenedioxycinnamyl alcohol (**11**)[13] and 3,4,5-trimethoxyphenylpropiolic acid (**12**)[14] were prepared through the scheme shown in Chart 3.

3-Methoxy-4,5-methylenedioxybenzaldehyde (**13**)[15] obtained from vanillin *via* 5-iodovanillin and 5-hydroxyvanillin was derived to the corresponding ethyl cinnamate (**14**) by means of the Wittig–Horner reaction[16] using triethyl phosphonoacetate in 90% yield. Compound **14** was subsequently reduced by lithium aluminum hydride (LAH) to afford **11** in 81% yield. On the other hand, **12** was obtained from 3,4,5-trimethoxybenzaldehyde *via* ethyl 3,4,5-trimethoxycinnamate (**15**) and the corresponding dibromo compound (**16**) followed by debromination. The process of bromination of **15** and subsequent debromination were achieved by Klemm's method.[14] The condensation of **11** and **12** was achieved by means of *N*,*N*-dicyclohexylcarbodiimide (DCC) in the presence of *p*-toluenesulfonic acid (*p*-TSA) in pyridine solution,[17] affording **17**, mp 140 °C, in 80% yield. Subsequent intramolecular Diels–Alder reaction of **17** was pursued in dimethylformamide (DMF) at elevated temperature.[18] In this reaction, the formation of three kinds of products, **18**, **19**, and **20**, is presumed (Fig. 2).

As a result, the reaction product was obtained as an amorphous powder. However, in the nuclear magnetic resonance (NMR) spectrum of this crude product, methylenedioxy group signals appeared at two different positions, *i.e.*, at δ 5.96 (J = 14.7 Hz) and at δ 5.69 (J = 25.5 Hz), suggesting that this product was a mixture of two compounds. The ratio of each component was found to be 1.8 : 1 from the integrated intensity of the methylenedioxy group signals. The mixture was subjected to silica gel column chromatography to afford two substances, **18** as major product and **19**. Compounds **18** and **19** showed the same molecular formula of $C_{23}H_{22}O_8$ and the same molecular weight of 426.1313 by high-resolution mass spectrometry (MS). In the NMR spectra, most of the signals of the two compounds were analogous. The signals of four methoxy groups appeared as three singlet peaks, showing the

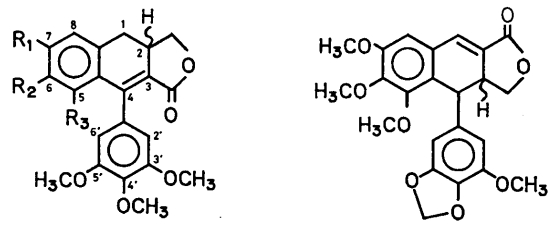
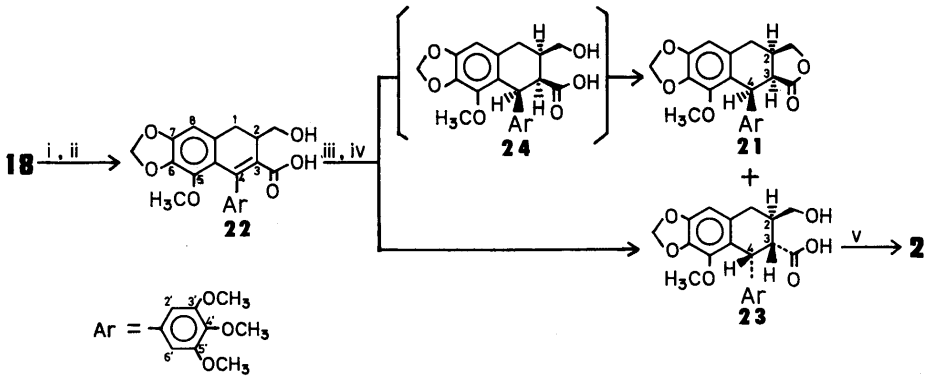


Fig. 2



i) 7% KOH; ii) neutralized with 2% HCl; iii) 10% Pd–C, H_2 4.5 atm, 45 °C; iv) conc. HCl; v) DCC.

Chart 4

existence of two equivalent methoxy groups, and no vinyl proton was observed. These facts rule out the existence of **20**. A methoxy group in **18** was observed at higher magnetic field (δ 3.35) than that of **19** (δ 3.95) due to the anisotropy of the trimethoxyphenyl group. Although it has been reported that the catalytic hydrogenation of analogous 1,2-dihydronaphthalene lactones usually gave phenyltetralin lactones with all-*cis* configurations,[18,19] we examined the direct hydrogenation of **18** expecting the formation of **2**, because no example was known of compounds which have any functional group on C-5. The reduction of **18** was carried out with 10% palladium carbon (Pd–C) in acetic acid for 4 h under atmospheric pressure. The reaction mixture was chromatographed on a silica gel column and an amorphous product (**21**) was obtained as a sole product in low yield with recovery of the starting material; compound **2** was not formed. Compound **21** was presumed to be isopicrohernandin by comparison of the NMR and infrared (IR) spectra with those of **2** and picrohernandin. The unsuccessful result of direct hydrogenation of **18** meant that a new strategy was required, and another method was worked out as described below (Chart 4).

The lactone ring of **18** was cleaved by potassium hydroxide and careful neutralization gave the unsaturated hydroxy acid (**22**). Crude **22** was hydrogenated on Pd–C in ethanol and the reaction mixture was subsequently acidified with concentrated hydrochloric acid. After usual work-up, the reaction mixture showed the existence of two compounds on thin layer chromatography (TLC) and each compound was isolated by preparative TLC (PTLC). One coincided with **21** obtained by the direct hydrogenation of **18** as judged from the NMR spectrum. Another compound (**23**) showed the existence of a hydroxy group in the IR spectrum (3480 cm^{-1}) and its molecular weight of 446 was confirmed by means of MS. The fact that **23** remained unlactonized in concentrated hydrochloric acid suggested that this hydroxy acid had a 2,3-*trans* configuration. It seems reasonable that the 2,3-*cis* hydroxy acid (**24**) would be more easily lactonized than the corresponding *trans* isomer (**23**) on account of the proximity of the hydroxy and carboxyl groups. Lactonization of **23** was achieved by means of DCC in chloroform solution[20] affording a crystalline compound of mp 215—218 °C (natural, mp 210—213 °C[2b]). All spectral deta were identical with those of natural hernandin.

In conclusion, (±)-hernolactone (**1**), and (±)-hernandin (**2**) with 2,3-*trans* and 3,4-*cis* configuration were synthesized.

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. The instruments used in this study were as follows; ultraviolet (UV) spectra, Hitachi 200-10 spectrometer; IR spectra, Jasco IR-810 spectrometer; MS, Hitachi M-80; ^{1}H-NMR spectra, Varian XL-300 and Gemini-200 instruments; ^{13}C-NMR spectra, Varian XL-300 instrument (with tetramethylsilane as an internal standard; chemical shifts are recorded in δ values). Column chromatography was carried out on Merck silica gel (Kieselgel 60; 70—230 mesh). Precoated silica gel plates used in PTLC were Merck Kieselgel 60 F_{254}, 0.5 mm thickness. The assignments of ^{13}C-NMR spectra were deduced by means of DEPT and HETCOR.[21]

4-*O*-Benzylsyringaldehyde (3) A mixture of syringaldehyde (5.91 g, 32.5 mmol), benzyl chloride (3.8 ml, 33.0 mmol), and anhydrous K_2CO_3 (2.99 g, 21.7 mmol) in DMF (30 ml) was heated at 110 °C for 16 h. The reaction mixture was filtered and the filtrate was added to AcOEt. The organic layer was washed with 10% NaOH and brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was left overnight to give pale yellow needles (8.11 g, 92%). mp 63.1—63.8 °C. *Anal.* Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.42; H, 5.94. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690 (C=O), 1130 (C–O–C). MS *m/z*: 272 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 3.90 (6H, s, $-OCH_3 \times 2$), 5.13 (2H, s, benzyl-CH_2), 7.11 (2H, s, arom. H), 7.31—7.48 (5H, m, arom. H), 9.86 (1H, s, –CHO).

4-Benzyloxy-3,5-dimethoxybenzaldehyde Bis(phenylthio)acetal (4) Benzenethiol (2.1 ml, 20.5 mmol) and BF_3·etherate (3.1 ml, 25.2 mmol) were added to a solution of **3** (2.72 g, 10.0 mmol) in dry $CHCl_3$ (30 ml) at −50 °C. The mixture was stirred at −50 °C for 25 min, poured into a little ice-water and extracted with $CHCl_3$. The organic layer was washed successively with 7% KOH, water and brine, and evaporated after drying over anhydrous K_2CO_3. The residue was recrystallized from isopropyl alcohol to give colorless needles (4.61 g, 89%). mp 71.5—74 °C. *Anal.* Calcd for $C_{28}H_{26}O_3S_2$: C, 70.85; H, 5.52. Found: C, 70.81; H, 5.47. IR ν_{max}^{KBr} cm^{-1}: 1583. MS *m/z* (rel. int.): 474 (M^+, 0.1), 365 ($M^+ - SPh$, 87.0). ^{1}H-NMR ($CDCl_3$) δ: 3.71 (6H, s, $-OCH_3 \times 2$), 4.98 (2H, s, benzyl-CH_2), 5.33 (1H, s, –CH–), 6.50 (2H, s, arom. H), 7.26—7.47 (15H, m, arom. H).

(±)-3-[4′-Benzyloxy-3′,5′-dimethoxy-α,α-bis(phenylthio)benzyl]butyrolactone (5) A solution of **4** (2.01 g, 4.24 mmol) in dry tetrahydrofuran (THF) (30 ml) was treated with *n*-BuLi (1.6 M in hexane solution, 3.0 ml) at −80 °C under nitrogen. The resulting yellow solution was stirred for 1 h. A solution of butenolide (0.33 ml, 4.71 mmol) in dry THF (15 ml) was added slowly over a period of 40 min. After 1 h, diluted HCl was added. The mixture was extracted with CH_2Cl_2. The extract was successively washed with water, saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The resulting yellow gum (2.6 g) was chromatographed (*n*-hexane–AcOEt, 2 : 1) to give crude **5**. Further purification was carried out using high-performance liquid chromatography (HPLC) (column, Cosmosil $5C_{18}$ (8 i.d. × 250 mm); eluent, CH_3CN; flow rate, 1.5 ml/min) to give **5** as a pale yellow solid (1.41 g, 60%). High-resolution MS Calcd for $C_{26}H_{25}O_5S$ ($M^+ - SPh$): 449.1421. Found: 449.1418. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1775 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.68 (1H, dd, J=18.0, 9.6 Hz, $-CH_2-C=O$), 2.92 (1H, dd, J=18.0, 7.8 Hz, $-CH_2-C=O$), 3.23 (1H, quint., $-CH_2-CH-CH_2-$), 3.70 (6H, s, $C_{3',5'}$-OCH_3),

4.43 (1H, dd, J=9.6, 8.1 Hz, –OC$\underline{H}_2$–), 4.46 (1H, dd, J=9.6, 7.5 Hz, –OC$\underline{H}_2$–), 5.05 (2H, s, benzyl-CH_2), 6.87 (2H, s, $C_{2',6'}$-H), 7.21—7.47 (15H, m, arom. H). ^{13}C-NMR ($CDCl_3$) δ: 32.01 (t, C_2-H_2), 43.91 (d, C_3-H), 56.26 (q, $C_{3',5'}$-OCH_3), 69.35 (t, C_4-H_2), 71.97 (s, C_5), 74.92 (t, benzyl-CH_2), 107.21 (d, $C_{2',6'}$-H), 127.97 (d), 128.13 (d), 128.53 (d), 128.87 (d), 129.09 (d), 131.26 (s), 131.45 (s), 133.22 (s), 134.65 (d), 134.94 (d), 136.76 (s), 137.46 (s), 153.08 (s), 175.68 (s, C_1=O).

(±)-*trans*-3-[4′-Benzyloxy-3′,5′-dimethoxy-α,α-bis(phenylthio)benzyl]-2-(3,4,5-trimethoxybenzyl)butyrolactone (6) **5** (446 mg, 0.8 mmol) was dissolved in dry THF (3 ml) under nitrogen. The solution was chilled to −80 °C, and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (0.21 ml, 1.0 mmol) was added slowly over 10 min. After 40 min, n-BuLi (1.6 M solution, 0.6 ml) was added over 30 min and the mixture was stirred for 1.5 h. Then a solution of hexamethylphosphoramide (HMPA) (0.17 ml, 0.98 mmol) and 3,4,5-trimethoxybenzyl bromide[5] (272 mg, 1.04 mmol) in THF (3 ml) was added and the whole was stirred at −80 °C for 4 h. The mixture was quenched with saturated aqueous NH_4Cl (10 ml) and extracted with AcOEt. The combined extract was washed successively with 10% HCl, water, saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (n-hexane–AcOEt, 2 : 1) to give **6** (458 mg, 78%) as a pale yellow solid. High-resolution MS Calcd for $C_{36}H_{37}O_8S$ (M^+ − SPh): 629.2206. Found: 629.2202. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.79 (1H, dd, J=13.8, 5.7 Hz, C_{6a}-H), 2.98 (1H, dt, J=8.1, 3.9 Hz, C_3-H), 3.18 (1H, dd, J=13.8, 4.2 Hz, C_{6b}-H), 3.38 (1H, dt, J=6.0, 4.2 Hz, C_2-H), 3.62 (1H, dd, J=9.9, 8.7 Hz, C_{4a}-H), 3.68 (s), 3.74 (s) (12H, $C_{3',5'}$-OCH_3 and $C_{3'',5''}$-OCH_3), 3.82 (3H, s, $C_{4''}$-OCH_3), 4.41 (1H, dd, J=9.9, 3.6 Hz, C_{4b}-H), 5.03 (2H, s, benzyl-CH_2), 6.23 (2H, s, $C_{2'',6''}$-H), 6.88 (2H, s, $C_{2',6'}$-H), 7.15—7.43 (15H, m, arom. H). ^{13}C-NMR ($CDCl_3$) δ: 37.37 (t, C_6-H_2), 44.84 (d, C_2-H), 47.74 (d, C_3-H), 56.15 (q, $C_{3'',5''}$-OCH_3), 56.28 (q, $C_{3',5'}$-OCH_3), 60.91 (q, $C_{4''}$-OCH_3), 68.38 (t, C_4-H_2), 73.37 (s, C_5), 75.00 (t, benzyl-CH_2), 106.35 (d, $C_{2'',6''}$-H), 107.06 (d, $C_{2',6'}$-H), 127.97 (d), 128.19 (d), 128.31 (d), 128.58 (d), 128.75 (d), 128.81 (d), 129.50 (d), 130.83 (s), 132.35 (s), 132.52 (s), 133.30 (d), 136.07 (d), 136.96 (s), 137.13 (s), 137.51 (s), 153.24 (s), 178.72 (s, C_1=O).

(±)-Hernolactone (1) **6** (431 mg, 0.58 mmol) was treated with a suspension of Raney Ni (W-4, 4 g) in absolute ethanol (50 ml) under reflux for 10 h. After filtration, the crude product was purified by PTLC (n-hexane–AcOEt, 2 : 3) (developed twice) to give **1** as a pale yellow solid (128 mg, 51%). Recrystallization from benzene–Et_2O gave needle crystals. mp 116—118 °C. *Anal.* Calcd for $C_{23}H_{28}O_8$: C, 63.88; H, 6.53. Found: C, 63.85; H, 6.54. UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 272 (3.25), 225 (4.19). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH), 1770 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.45—2.68 (4H, m, $C_{2,3}$-H and C_5-H_2), 2.94 (2H, m, C_6-H_2), 3.81 (s), 3.83 (s) (15H, $C_{3',5'}$-OCH_3 and $C_{3'',4'',5''}$-OCH_3), 3.90 (1H, dd, J=9.3, 7.5 Hz, $C_{4\beta}$-H), 4.20 (1H, dd, J=9.3, 7.2 Hz, $C_{4\alpha}$-H), 5.41 (1H, s, $C_{4'}$-OH, disappeared on addition of D_2O), 6.21 (2H, s, $C_{2',6'}$-H), 6.35 (2H, s, $C_{2'',6''}$-H). ^{13}C-NMR ($CDCl_3$) δ: 35.16 (t, C_6-H_2), 38.81 (t, C_5-H_2), 41.25 (d, C_3-H), 46.48 (d, C_2-H), 56.16 (q, $C_{3'',5''}$-OCH_3), 56.28 (q, $C_{3',5'}$-OCH_3), 60.86 (q, $C_{4''}$-OCH_3), 71.26 (t, C_4-H_2), 105.27 (d, $C_{2',6'}$-H), 106.31 (d, $C_{2'',6''}$-H), 128.98 (s, $C_{1'}$), 133.50 (s, $C_{1''}$), 133.65 (s, $C_{4'}$), 136.99 (s, $C_{4''}$), 147.19 (s, $C_{3',5'}$), 153.34 (s, $C_{3'',5''}$), 178.65 (s, C_1=O). MS m/z (rel. int.): 432 (M^+, 100), 251 (3.4), 238 (2.0), 208 (0.9), 194 (2.9), 181 (88.9), 167 (54.7), 151 (8.5).

Ethyl 3-Methoxy-4,5-methylenedioxycinnamate (14) A mixture of **13** (495 mg, 2.75 mmol), triethyl phosphonoacetate (0.65 ml, 3.3 mmol), anhydrous K_2CO_3 (760 mg, 5.5 mmol) and water (0.55 ml) was stirred at 85 °C for 5 h. The mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was recrystallized from n-hexane to give colorless needles (621 mg, 90%). mp 76 °C. *Anal.* Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.17; H, 5.61. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O), 925 (–OCH_2O–). MS m/z: 250 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7.2 Hz, –$OCH_2C\underline{H}_3$), 3.94 (3H, s, C_3-OCH_3), 4.27 (2H, q, J=7.2 Hz, –$OC\underline{H}_2CH_3$), 6.03 (2H, s, –OCH_2O–), 6.29 (1H, d, J=16 Hz, Ph-CH=C$\underline{H}$–), 6.71 (1H, d, J=1.2 Hz, C_6-H), 6.76 (1H, d, J=1.2 Hz, C_2-H), 7.57 (1H, d, J=16 Hz, Ph-C$\underline{H}$=CH–).

3-Methoxy-4,5-methylenedioxycinnamyl Alcohol (11) LAH (1.2 g, 32 mmol) was added in four portions during 0.5 h to a stirred solution of **14** (2.51 g, 10.0 mmol) in dry Et_2O (90 ml) at −15 °C under nitrogen. Stirring was continued for 2.5 h, then the solution was poured into water and extracted with AcOEt. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and evaporated. Recrystallization of the residue from CCl_4 gave fine pale yellow crystals (1.70 g, 81%). mp 77—81 °C (lit.[13a] 79 °C,[13b] 80—81 °C). *Anal.* Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.16; H, 5.73. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 930 (–OCH_2O–). MS m/z: 208 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.50 (1H, br, –OH, disappeared on addition of D_2O), 3.91 (3H, s, C_3-OCH_3), 4.30 (2H, dd, J=6.0, 1.2 Hz, –$C\underline{H}_2OH$), 5.96 (2H, s, –OCH_2O–), 6.21 (1H, dt, J=16, 6.0 Hz, Ph-CH=C$\underline{H}$–), 6.50 (1H, d, J=16 Hz, Ph-C$\underline{H}$=CH–), 6.55 (1H, s, C_6-H), 6.62 (1H, s, C_2-H).

Ethyl 3,4,5-Trimethoxycinnamate (15) A mixture of 3,4,5-trimethoxybenzaldehyde (2.00 g, 10.2 mmol), anhydrous K_2CO_3 (2.76 g, 20.0 mmol), triethyl phosphonoacetate (2.4 ml, 12 mmol) and water (2.0 ml) was stirred at 70 °C for 4 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and evaporated. Recrystallization of the residue from n-hexane yielded **15** (2.45 g, 90%) as colorless needles. mp 68—69.5 °C (lit.[22] 67 °C). *Anal.* Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.86; H, 6.77. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (C=O). MS m/z: 266 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.2 Hz, –$OCH_2C\underline{H}_3$), 3.88 (3H, s, C_4-OCH_3), 3.89 (6H, s, $C_{3,5}$-OCH_3), 4.27 (2H, q, J=7.2 Hz, –$OC\underline{H}_2CH_3$), 6.35 (1H, d, J=16 Hz, Ph-CH=C$\underline{H}$–), 6.76 (2H, s, $C_{2,6}$-H), 7.61 (1H, d, J=16 Hz, Ph-C$\underline{H}$=CH–).

Ethyl 2,3-Dibromo-3-(3,4,5-trimethoxyphenyl)propionate (16) A solution of Br_2 (1.0 ml, 19.4 mmol) in $CHCl_3$ (12 ml) was gradually added (40 min) to a stirred ice-cold solution of **15** (4.81 g, 18.1 mmol) in $CHCl_3$ (24 ml). Stirring was continued for 1 h at 0 °C, then the solution was evaporated and recrystallized from n-hexane–CCl_4 to give a colorless crystalline powder (4.93 g, 64%). mp 105—106 °C. *Anal.* Calcd for $C_{14}H_{18}Br_2O_5$: C, 39.46; H, 4.26. Found: C, 39.15; H, 4.10. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (C=O). MS m/z: 426 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7.2 Hz, –$OCH_2C\underline{H}_3$), 3.87 (3H, s, C_4-OCH_3), 3.89 (6H, s, $C_{3,5}$-OCH_3), 4.37 (2H, q, J=7.2 Hz, –$OC\underline{H}_2CH_3$), 4.80 (1H, d, J=11.6 Hz, Ph-CH–C$\underline{H}$–), 5.29 (1H, d, J=11.6 Hz, Ph-C$\underline{H}$–CH–), 6.62 (2H, s, $C_{2,6}$-H).

3,4,5-Trimethoxyphenylpropiolic Acid (12) A mixture of **16** (5.30 g, 12.4 mmol), saturated aqueous KOH (2.2 g, 39 mmol) and EtOH (13 ml) was refluxed for 8 h. The solution was poured into ice-water and acidified with concentrated HCl. After standing for 4 h at 0 °C, the solution was filtered and the precipitate was recrystallized from CCl_4 to give **12** (1.64 g, 56%) as colorless needles. mp 138—140 °C (lit.[14] 140—141 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2210 (C≡C), 1690 (C=O). MS m/z: 236 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 3.71 (3H, s, C_4-OCH_3), 3.81 (6H, s, $C_{3,5}$-OCH_3), 6.95 (2H, s, $C_{2,6}$-H), 13.7 (1H, br, COOH, disappeared on addition of D_2O).

3-Methoxy-4,5-methylenedioxycinnamyl 3′,4′,5′-Trimethoxyphenylpropiolate (17) **11** (1.87 g, 8.98 mmol), **12** (2.13 g, 9.02 mmol) and p-TSA (90 mg) were dissolved in dry pyridine (22.5 ml) under nitrogen. A solution of DCC (2.04 g, 9.89 mmol) in dry pyridine (6.8 ml) was added and the whole was stirred at room temperature for 26 h. AcOH (9 ml) was added, and the mixture was allowed to stand at 0 °C for 4 h and filtered. The precipitate was washed with cold pyridine. The filtrate was acidified with concentrated HCl and extracted with a mixture of Et_2O–AcOEt (1 : 1). The extract was washed with water, 7% K_2CO_3, water and brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was recrystallized from CCl_4 to yield **17** (3.05 g, 80%) as colorless prisms. mp 140—143 °C. *Anal.* Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.70; H, 5.19. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2200 (C≡C), 1700 (C=O), 920 (–OCH_2O–). MS m/z: 426 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 3.86 (6H, s, $C_{3',5'}$-OCH_3), 3.89 (s), 3.91 (s) (6H, C_3-OCH_3 and C_4-OCH_3), 4.86 (2H, d, J=6.9 Hz, –CH=CH–C$\underline{H}_2$–), 5.98 (2H, s, –OCH_2O–), 6.18 (1H, dt, J=16, 6.9 Hz, –CH=C$\underline{H}$–CH_2–), 6.57 (1H, s, C_6-H), 6.61 (1H, d, J=16 Hz, –C$\underline{H}$=CH–CH_2–), 6.64 (1H, s, C_2-H), 6.84 (2H, s, $C_{2',6'}$-H).

(±)-2-Hydroxymethyl-5-methoxy-6,7-methylenedioxy-4-(3′,4′,5′-trimethoxyphenyl)-1,2-dihydro-3-naphthoic Acid Lactone (18) A solution of **17** (1.98 g, 4.65 mmol) in DMF (127 ml) was refluxed for 6 h, then poured into water and extracted with $CHCl_3$. The extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated. The products were separated by column chromatography (n-hexane–AcOEt–$CHCl_3$, 2 : 1 : 1) to give **18** and **19**. Recrystallization of the amorphous powder of **18** from $CHCl_3$–MeOH gave colorless prisms (0.75 g, 38%). mp 270.5—271.5 °C. **19** was recrystallized from MeOH, affording yellow prisms. mp 263—267 °C. **18**: *Anal.* Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.69; H, 5.19. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (C=O), 930 (–OCH_2O–). MS m/z: 426 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.66—2.92 (2H, m, C_1-H), 3.25—3.35 (1H, m, C_2-H), 3.35 (3H, s, C_5-OCH_3), 3.84 (6H, s, $C_{3',5'}$-OCH_3), 3.89 (3H, s, $C_{4'}$-OCH_3), 3.97 (1H, dd, J=9.0, 7.7 Hz, lactone-CH_2), 4.64 (1H, pseudo t, J=9.0 Hz, lactone-CH_2), 5.96 (2H, dd, J=14.7, 1.4 Hz, –OCH_2O–), 6.54 (3H, br s, $C_{8,2',6'}$-H). **19**: High-resolution MS Calcd for $C_{23}H_{22}O_8$ (M^+): 426.1313. Found: 426.1315. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (C=O), 920 (–OCH_2O–). ^{1}H-NMR ($CDCl_3$) δ: 2.70—2.97 (2H, m, C_1-H), 3.30—3.45 (1H, m, C_2-H), 3.83 (6H, s, $C_{3',5'}$-OCH_3), 3.91 (3H, s, $C_{4'}$-OCH_3), 3.95 (3H, s, C_7-OCH_3), 4.00 (1H,

pseudo t, J=9.0 Hz, lactone-CH_2), 4.68 (1H, pseudo t, J=9.0 Hz, lactone-CH_2), 5.69 (2H, dd, J=25.5, 1.2 Hz, $-OCH_2O-$), 6.48 (1H, s, C_8-H), 6.60 (2H, br s, $C_{2',6'}$-H).

(±)-Isopicrohernandin (21) A solution of **18** (85 mg, 0.20 mmol) in AcOH (15 ml) was stirred with 10% Pd–C (50 mg) under H_2 gas at 65—70 °C and atmospheric pressure for 4 h. After removal of the catalyst by filtration, the filtrate was poured into water and extracted with $CHCl_3$. The organic layer was washed with water and brine, dried and evaporated. The residue was purified by column chromatography (benzene–MeOH, 10 : 1) to give **21** (23 mg, 27%) as an amorphous powder. Recrystallization from AcOEt gave colorless prisms. mp 275—276 °C. *Anal.* Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.29; H, 5.62. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (C=O), 940 ($-OCH_2O-$). MS *m/z* (rel. int.): 428 (M^+, 100), 313 (12.1), 260 (20.1), 203 (8.6), 181 (11.9), 165 (5.4). ^{1}H-NMR ($CDCl_3$) δ: 2.64—2.75 (1H, m, C_1-H), 2.86—3.00 (2H, m, $C_{1,3}$-H), 3.00—3.20 (1H, m, C_2-H), 3.28 (1H, pseudo t, J=8.5 Hz, lactone-CH_2), 3.73 (6H, s, $C_{3',5'}$-OCH_3), 3.80 (3H, s, $C_{4'}$-OCH_3), 3.90 (3H, s, C_5-OCH_3), 4.37 (1H, pseudo t, J=8.5 Hz, lactone-CH_2), 5.10 (1H, d, J=6.0 Hz, C_4-H), 5.96 (2H, dd, J=6.9, 1.4 Hz, $-OCH_2O-$), 6.35 (2H, s, $C_{2',6'}$-H), 6.49 (1H, s, C_8-H).

(±)-2-Hydroxymethyl-5-methoxy-6,7-methylenedioxy-4-(3',4',5'-trimethoxyphenyl)-1,2-dihydro-3-naphthoic Acid (22) A solution of **18** (100 mg, 0.23 mmol) in MeOH (30 ml) was stirred with KOH (2.1 g) at 50 °C for 5 h. The solution was poured into water and extracted with $CHCl_3$ to remove neutral material. The aqueous layer was carefully neutralized with 2% HCl at 0 °C and extracted with Et_2O. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and evaporated to give **22** (96 mg, 94%) as an amorphous powder. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1730 (C=O), 930 ($-OCH_2O-$). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.60—3.15 (3H, m, $C_{1,2}$-H), 3.30 (3H, s, C_5-OCH_3), 3.40—3.79 (2H, m, $-CH_2OH$), 3.79 (6H, s, $C_{3',5'}$-OCH_3), 3.83 (3H, s, $C_{4'}$-OCH_3), 5.92 (2H, d, J=9.4 Hz, $-OCH_2O-$), 6.40 (2H, s, $C_{2',6'}$-H), 6.46 (1H, s, C_8-H), 7.30 (1H, br, –OH, disappeared on addition of D_2O).

(±)-Hernandin (2) A solution of **22** (59 mg, 0.13 mmol) in EtOH (25 ml) was shaken with 10% Pd–C (59 mg) under H_2 gas at 45 °C and 4.5 atmospheres pressure for 24 h. The catalyst was filtered off, and the solution was acidified with concentrated HCl and extracted with Et_2O. The organic layer was washed with water and brine, dried and evaporated. The residue was separated by PTLC ($CHCl_3$–AcOEt, 10 : 1) to give **21** (23 mg, 40%, *Rf* 0.5) and **23** (14 mg, 24%, *Rf* 0.1). **21** was identified by direct comparison with the authentic sample obtained by direct hydrogenation of **18**. **23**: Amorphous powder. High-resolution MS Calcd for $C_{23}H_{26}O_9$ (M^+): 446.1575. Found: 446.1575. IR ν_{max}^{KBr} cm^{-1}: 3480 (OH), 1730 (C=O), 925 ($-OCH_2O-$). ^{1}H-NMR ($CDCl_3$) δ: 1.65 (1H, br, $-CH_2OH$, disappeared on addition of D_2O), 2.30—2.50 (1H, m, C_2-H), 2.68—2.81 (1H, m, C_3-H), 2.90—3.08 (2H, m, C_1-H), 3.57 (3H, s, C_5-OCH_3), 3.69 (2H, pseudo t, J=4.5 Hz, $-CH_2OH$), 3.74 (6H, s, $C_{3',5'}$-OCH_3), 3.79 (3H, s, $C_{4'}$-OCH_3), 4.72 (1H, d, J=5.7 Hz, C_4-H), 5.89 (2H, dd, J=3.2, 1.4 Hz, $-OCH_2O-$), 6.25 (2H, s, $C_{2',6'}$-H), 6.42 (1H, s, C_8-H). A solution of **23** (14 mg, 0.031 mmol) and DCC (12 mg, 0.058 mmol) in $CHCl_3$ (6 ml) was stirred at room temperature for 5 h. The solution was evaporated and the residue was purified by PTLC (benzene–MeOH, 97 : 3) to give **2** (9 mg, 15%) as an amorphous powder. Recrystallization from EtOH gave colorless prisms. mp 215—218 °C. High-resolution MS Calcd for $C_{23}H_{24}O_8$ (M^+): 428.1470. Found: 428.1472. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1775 (C=O), 945 ($-OCH_2O-$). MS *m/z* (rel. int.): 428 (M^+, 100), 260 (6.4), 215 (9.1), 203 (25.1), 181 (30.0), 165 (10.3). ^{1}H-NMR ($CDCl_3$) δ: 2.56—2.82 (3H, m, $C_{1,2,3}$-H), 3.00—3.15 (1H, m, C_1-H), 3.63 (3H, s, C_5-OCH_3), 3.76 (6H, s, $C_{3',5'}$-OCH_3), 3.81 (3H, s, $C_{4'}$-OCH_3), 3.89 (1H, pseudo t, J=8.7 Hz, lactone-CH_2), 4.45 (1H, dd, J=8.7, 6.0 Hz, lactone-CH_2), 4.87 (1H, d, J=4.6 Hz, C_4-H), 5.93 (2H, dd, J=7.6, 1.4 Hz, $-OCH_2O-$), 6.38 (2H, s, $C_{2',6'}$-H), 6.44 (1H, s, C_8-H).

Acknowledgements We are indebted to Miss M. Nabae and Miss M. Danjyo for measurements of NMR spectra and MS, and Mrs. Y. Tsukamoto for elemental analyses.

References and Notes

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